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4-FACTOR PROTHROMBIN COMPLEX CONCENTRATE ADMINISTRATION VIA INTRAOSSEOUS ACCESS FOR URGENT REVERSAL OF WARFARIN

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☐ **Abstract—Background: Vitamin K antagonist (VKA) reversal in patients with acute major bleeding and coagulopathy is an example of an urgent intervention in the emergency department. Intravenous (IV) prothrombin complex concentrate (PCC) may reverse VKA-induced coagulopathy in <30 min. In patients lacking IV access, effective PCC administration becomes problematic. No previous case reports have documented PCC infusion via intraosseous (IO) or alternative routes in this setting. Case Report: A 74-year-old man presented to the emergency department (ED) after a head injury, with sudden onset of left-sided facial droop, weakness, hypertension, and dizziness. Initial vital signs include blood pressure of 221/102 mm Hg, a heart rate of 75 beats/min, and oxygen saturation of 96% on room air. Warfarin 3 mg once daily was among his medications. His international normalized ratio (INR) was 3.9 with a computed tomography scan showing intraparenchymal hemorrhage in the right temporal lobe. Multiple attempts for IV access at various sites were unsuccessful. Therefore, IO access was established. Because of his prolonged prothrombin time, elevated INR, and intraparenchymal hemorrhage, the decision was made to use 4-factor PCC to reverse the supratherapeutic INR. The INR normalized as an emergent right parietal hematoma evacuation was performed. After an inpatient course, the patient was eventually discharged. Why Should an Emergency Physician Be Aware of This?: VKAs, like warfarin, are commonly prescribed medications. When life-threatening hemorrhage is present, rapid reversal of a VKA-induced coagulopathy may be a life-saving therapy. In the event that IV access has not been established, we have demonstrated that IO access is a viable alternative route for PCC administration. Published by Elsevier Inc.**

☐ **Keywords—bleeding; prothrombin complex concentrate; reversal; vitamin K antagonist**

INTRODUCTION

Warfarin is a vitamin K antagonist (VKA) that inhibits the synthesis of vitamin K–dependent clotting factors, including factors II, VII, IX, and X and anticoagulant proteins C and S (1). Vitamin K is an essential cofactor for the synthesis of these clotting factors and induces a dose-dependent acquired deficiency of these factors, leading to impaired coagulation. Warfarin is used as an anticoagulant for thromboembolic prophylaxis or treatment or myocardial risk reduction. Inappropriate dosing or monitoring may lead to an increased risk of bleeding. Before direct oral anticoagulants (DOACs) like dabigatran, rivaroxaban, apixaban, and edoxaban were brought onto the market in 2010, an estimated 1.6% of the U.S. population was taking an oral VKA like warfarin (2,3). DOACs have led to decreased VKA utilization. However, >18 million prescriptions were written for warfarin in 2016 (4).

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Kcentra (CSL Behring, King of Prussia, PA) is nonactivated 4-factor prothrombin complex concentrate (PCC) made from pooled human plasma. It contains vitamin K–dependent coagulation factors II, VII, IX, and X (which constitute the prothrombin complex), and antithrombotic proteins C and S (5,6). The administration of Kcentra rapidly increases the levels of vitamin K–dependent coagulation factors.

CASE REPORT

A 74-year-old man who lived independently and had a preillness modified Rankin scale score of 3 called emergency medical service (EMS) assistance with right lower quadrant pain. During transport, he had sudden onset of left-sided facial droop and weakness. The patient's family stated, upon their arrival to the emergency department (ED), that the patient had suffered a blow to his head before calling EMS. His medical history included atrial fibrillation and hypertension. His medications included warfarin 3 mg by mouth daily. His surgical history included a partial hip replacement in July 2018. A review of systems were positive for abdominal pain, facial asymmetry, speech difficulty, weakness, and confusion. On physical examination, the patient appeared lethargic. Right and left pupils were not reactive. Cranial nerve and sensory deficit were present. There was a left-sided flaccid paralysis. His Glasgow Coma Scale (GCS) score was 13. On arrival to the ED, his blood pressure was 221/102 mm Hg, his heart rate was 75 beats/min, and his oxygen saturation was 96% on room air. The patient weighed 72.7 kg. The initial laboratory findings included several pertinent abnormal values, including a prothrombin time/international normalized ratio of 43.1 s/3.9, and an activated partial thromboplastin time of 40.9 s.

Hemorrhagic stroke was suspected. A computed tomography scan revealed a 7.2- × 3.5-cm intraparenchymal hemorrhage in the right temporal lobe with a mass effect and a 5.7-mm midline shift from right to left, with moderate subfalcine herniation. However, multiple attempts at achieving peripheral and central intravenous (IV) access—via the left and right femoral and left and right internal jugular veins—in the ED failed. We believe attempts at IV access may have failed because of calcified vasculature, as the guidewire could not be advanced at any sites.

Because of the elevated INR and intraparenchymal brain hemorrhage, the decision was made to use PCC to reverse the supratherapeutic INR. Our institution stocks the 4-factor PCC product Kcentra.

Kcentra was therefore initiated at a dose of 2000 units (25 units/kg rounded to the nearest 500 units) via intraosseous (IO) needle. The medication was diluted in 80 mL of fluid and infused at a rate of 500 mL/h. The tubing was then flushed with 50 mL of normal saline at the same rate. This infusion was followed by 10 mg phytondione (vitamin K), given over 1 h as the patient was transferred to a level I trauma center for emergent right parietal craniotomy and hematoma evacuation. On arrival to the trauma center, his INR was 1.1 at 90 minutes after PCC infusion.

With supportive care, his GCS score was 5t (t = endotracheal intubation) 1 day after neurosurgical intervention. Three days later his GCS score was 9t. By day 4, the patient was no longer mechanically ventilated and from days 4–10 his GCS score wavered between 14 and 15 with some waxing and waning confusion. After 10 days, the patient was transferred from intensive care to a general floor. Fifteen days after presentation to the ED, the patient was discharged to a skilled nursing facility. At discharge, the patient had a modified Rankin scale score of 4. While described as alert, pleasant, co-operative, and oriented to person, place, and time, he did require assistance with activities of daily living. Within 2 weeks of skilled nursing facility admission, the patient was discharged to live with family.

DISCUSSION

States of hemorrhage or dehydration or numerous previous IV access episodes can lead to collapse of the peripheral veins and difficulty obtaining any IV access (7). The IO space represents an alternative site for IV access because it represents a noncollapsible entry point into systemic circulation. In the middle of the diaphysis is a vast central sinus, composed of distensible endothelium, that can accommodate a five-fold increase in volume (8). The vasculature of the IO space is connected to systemic circulation by a series of longitudinal Haversian canals containing a small artery and a vein, which are linked to a system of Volkmann canals. The Volkmann canals penetrate the cortex and terminate in connections with the osseous venous drainage. In adults, indicated access sites include the proximal humerus and the proximal and distal tibia (9). The proximal tibia ultimately drains into the popliteal vein and the distal tibia drains into the saphenous vein, with the proximal humerus connecting to the axillary vein. With need for intravascular access, IO access was established at the left proximal tibia of our patient.

Fresh frozen plasma and 3-factor PCC have safely been given via IO access (10–12). While there are no case reports or information in the literature describing 4-factor PCC via the IO route, the urgency of the situation and the similarity of 4-factor PCC with other agents with established safety suggested the appropriateness of 4-PCC in this case.

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

This case represents the first occurrence described in the literature of using the 4-factor PCC agent Kcentra via IO access to effectively reverse INR for the U.S. Food and Drug Administration–approved indication of urgent reversal of acquired factor deficiency induced by VKA therapy. The urgency of giving a reversal agent for warfarin in the ED for a multitude of etiologies may be profound. In the event that IV access cannot be attained, this case may provide guidance of an alternative route for a potentially life-saving medical intervention. Further studies are needed to re-evaluate and confirm the effectiveness of this practice.

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